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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/936,019	09/07/2001	Radmila Micanovic	X-13161	9268

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ELI LILLY AND COMPANY
PATENT DIVISION
P.O. BOX 6288
INDIANAPOLIS, IN 46206-6288

EXAMINER

O HARA, EILEEN B

ART UNIT	PAPER NUMBER
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1646

DATE MAILED: 12/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/936,019	Applicant(s) MICANOVIC ET AL.	
	Examiner Eileen O'Hara	Art Unit 1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 23 October 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-10, 12-16 and 21 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-10, 12-16 and 21 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____. |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>4</u> . | 6) <input type="checkbox"/> Other: _____. |

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DETAILED ACTION

1. Claims 1-10, 12-16 and 21 are pending in the instant application. Claims 11, 17-20, 22 and 23 have been canceled as requested by Applicant in Preliminary Amendment A, Paper No. 3

All claims are currently under examination.

Election/Restrictions

2. Applicant's election of the species of claim 21 in the Paper filed Oct. 28, 2003 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Priority

3. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) and 120 as follows: An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78). There is a blank space where "60/178,184" should be.

Specification

4. The disclosure is objected to because of the following informalities: There is a blank after "Serial No." on the first line of page 3.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-10, 12-16 and 21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a FLINT analog having Arg at amino acid 218 of the protein of SEQ ID NO: 1 substituted with another amino acid and resistant to proteolysis *in vivo* or a FLINT analog having Arg at amino acid 218 of the protein of SEQ ID NO: 1 substituted with another amino acid and resistant to proteolysis by thrombin *in vitro*, does not reasonably provide enablement for FLINT analogs that are resistant to proteolysis (*in vivo* or *in vitro*) having the amino acid sequence of SEQ ID NO: 1 except for replacement of amino acid 214, 215, 216, 217, 219, 220, 221 or 222 (or combinations thereof) with any other amino acid. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The instant specification teaches that the FLINT polypeptide having the amino acid sequence of SEQ ID NO: 1 (mature form, 271 amino acids) or SEQ ID NO: 3 (native form, 300 amino acids), is proteolytically cleaved *in vivo* after amino acid 218 of SEQ ID NO: 1 to produce two fragments, one comprising amino acids 1-218 (designated FLINT metabolite) and the other comprising amino acids 219-271. The specification provides the results of several experiments in which Arg at position 218 of SEQ ID NO: 1 is replaced with another amino acid, which results in a protein that is not proteolytically cleaved when produced recombinantly by cells in

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culture (pages 57-60), which is not cleaved by thrombin (Fig. 1), and which is not proteolytically cleaved in mouse blood *in vitro* (Fig. 5) or after intravenous administration in mice (Fig. 6). The data demonstrate that the non-proteolytically cleaved form is retained in blood and serum longer than the cleaved form. The specification also provides experiments in which the non-cleaved form of FLINT binds to FAS ligand comparably to that of the cleaved form and inhibits apoptosis *in vitro* (Fig. 2-4, table on page 61) and protects mice from death in a mouse acute liver failure model (Fig. 7). Therefore, the specification is enabling for a FLINT analog that has Arg at amino acid 218 of SEQ ID NO: 1 replaced with another amino acid, since all of the experiments were done with variants of SEQ ID NO: 1 having at least that substitution (some of the experiments were also done with FLINT variants also having amino acid substitutions at different amino acids in addition to the substitution of amino acid 218). However, there were no experiments performed with any FLINT variant not having the Arg at amino acid 218 replaced by another amino acid, and the claims encompass other variants in which the Arg at amino acid 218 is retained but other amino acids at positions 214-217 and 219-222 are substituted, and it is not predictable that substituting the amino acids at any of these other positions would result in a FLINT variant that would be protease resistant. The specification does not disclose what protease cleaves the FLINT protein *in vivo*, however, the *in vitro* experiments demonstrate that thrombin cleaves the protein, and thrombin is also present in blood and serum, in which experiments were done. Thrombin is possibly be the protease that cleaves the protein of SEQ ID NO: 1. Suidan et al., Proc. Natl. Acad. Sci. SUA, Vol. 91, pages 8112-8116, August 1994, teaches that the authentic thrombin cleavage site has the amino acid sequence Leu-Asp-Pro-Arg-Ser (abstract). Dawson et al., WO 91/09118, June 27, 1991, pages 12, teaches that the structure

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required for recognition by thrombin appears to be partially determined by local amino acid sequence around the cleavage site but is also determined to a variable extent by sequence(s) remote from the cleavage site, and gives as an example the fibrinogen A alpha chain. Dawson et al. also teaches that comparative studies of several proteins and peptides which are cleaved by thrombin has led to the proposal that optimum cleavage sites for α -thrombin may have the structure of (i) P4-P3-Pro-Arg-P1'-P2', where each of P3 and P4 is independently a hydrophobic amino acid (such as valine) and each of P1' and P2' is independently a non-acidic amino acid such as a hydrophobic amino acid like valine, or (ii) P2-Arg-P1', where P2 or P1' is glycine, but that there are exceptions to these general structures which are cleaved by thrombin.

From these teachings, it appears that the critical amino acid which is essential for thrombin cleaving activity is Arg, amino acid 218 of SEQ ID NO: 1, and that amino acids 215, 216, 217, 219 and 200 can be varied and may still retain an active thrombin cleavage site, depending upon what amino acid is substituted. Therefore, the specification and the prior art are enabling for a thrombin resistant FLINT polypeptide in which Arg of position 218 can be substituted and which would result in an *in vivo* or thrombin (protease) resistant protein. From the prior art and the teachings of the specification, it is not predictable that substitutions at any one of amino acids 214-217 or 219-222 would produce a thrombin resistant protein, and the prior art teaches that amino acid substitutions could be made in these amino acids and the resulting protein would not be thrombin (protease) resistant.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of

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predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (FED. Cir. 1988).

It is acknowledged that the level of skill in the art is high. However, there is no example of a protease resistant FLINT analog that does not have Arg of amino acid 218 of SEQ ID NO: 1 substituted with a different amino acid, the prior art teaches that the amino acids immediately around the Arg of the thrombin cleavage site may be changed and yet may still be cleaved. It is not predictable which amino acids or combinations of amino acids would result in a protease resistant FLINT analog. The instant claims are drawn to proteins which may or may not be protease resistant, and the instant specification has not provided adequate guidance on which amino acids may be substituted. In the instant situation, the teachings of the specification do not correspond in scope to those used to describe and define the subject matter claimed. Because it is not predictable which amino acids may be substituted, undue experimentation would be required to practice the invention. Due to the large quantity of experimentation necessary to determine which amino acid substitutions would produce a protease resistant FLINT analog, the lack of direction/guidance presented in the specification, the absence of working examples except for substitution at amino acid 218, the complex nature of the invention, the state of the prior art which teaches that many different amino acid substitutions can be made in the thrombin cleavage site which render the protein cleavable, and the breadth of the claims, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Conclusion

6.1 No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (703) 308-3312. The examiner can normally be reached on Monday through Friday from 10:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached at (703) 308-6564.

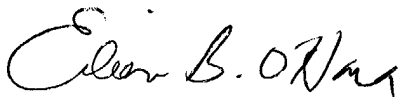
Official papers Before Final filed by RightFax should be directed to (703) 872-9306.

Official papers After Final filed by RightFax should be directed to (703) 872-9307.

Official papers filed by fax should be directed to (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Eileen B. O'Hara, Ph.D.

A handwritten signature in black ink, appearing to read "Eileen B. O'Hara". The signature is fluid and cursive, with the first name "Eileen" being more prominent.

Patent Examiner